Journal Pre-proof

SARS-CoV-2 infection in patients with neuroimmunological disorders in a tertiary referral centre from the north of Portugal.

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Please cite this article as: João Moura , Henrique Nascimento , Inês Ferreira , Raquel Samões , Catarina Teixeira , Dina Lopes , Daniela Boleixa , Ana Paula Sousa , Ernestina Santos , Ana Martins Silva , SARS-CoV-2 infection in patients with neuroimmunological disorders in a tertiary referral centre from the north of Portugal., *Multiple Sclerosis and Related Disorders* (2022), doi: https://doi.org/10.1016/j.msard.2022.103893

Highlights

- Older age appears to be the most implicated factor in COVID-19 severity in patients with neuroimmunological disorders.
- We found no association between disease modifying therapy and outcome.
- COVID-19 mortality rate appears to be greater in patients with neuroimmunological disorders compared to the general population.
- Recognizing the risk factors for severe COVID-19 in patients with neuroimmunological disorders could help to improve treatment decision making and appropriate monitoring strategies.

SARS-CoV-2 infection in patients with neuroimmunological disorders in a tertiary referral centre from the north of Portugal.

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Abstract

Introduction: The impact of COVID-19 in patients with neuroimmunological disorders is not fully established. There is some evidence suggesting an increased risk of more severe infection associated with the use of immunosuppressors in this population.

Objective: To characterize SARS-CoV-2 infection in patients followed in the neuroimmunology outpatient clinic of a tertiary centre from the north of Portugal.

Methods: Retrospective analysis of neuroimmunological patients with PCR-proven SARS-CoV-2 infection during the observational period of 20 months.

Results: Ninety-one patients were infected, 68.1% female, with a mean age of 48.9 ± 16.7 years. The median disease duration was 11.0 (IQR 6.0-19.0) years. Sixty-one patients (67.0%) had Multiple Sclerosis, of which 50 with relapsing-remitting course, 12 (13.2%) Myasthenia Gravis (MG), 6 (6.6%) Autoimmune Encephalitis and 6 (6.6%) Chronic Inflammatory Demyelinating Polyneuropathy. Seventy-six patients (83.5%) were taking disease-modifying therapy, 77.6% of which were on immunosuppressants, including anti-CD20 in 12 (13.2%). Most patients had mild COVID-19 (84.6%), with 3 cases (3.3%) of severe disease and, 7 cases (7.7%) of critical disease being reported. In total, 13 patients were hospitalized and 4 died. Patients with severe to critical disease were significantly older than patients with milder forms (69.4 ± 21.0 versus 46.5 ± 14.4 years, $p < 0.01$). MG was also associated with more severe disease ($p = 0.02$). There was

no association between comorbidities or use of immunosuppressors (including anti-CD20) and COVID-19 severity.

Conclusions: Greater age and MG were associated with severe or critical COVID-19. We found no association between a specific DMT, including anti-CD20, and outcome. Clinical recovery was achieved by 93.4%.

Keywords

Neuroimmunology; Multiple Sclerosis; COVID-19.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic posed several challenges for patients with preceding neurological conditions. Given its impact on both the immune and nervous systems, it is particularly relevant to study coronavirus disease 2019 (COVID-19) in patients with neuroimmunological disorders. Moreover, these diseases are caused by dysregulation of immune tolerance and require either immunosuppressive or immunomodulatory therapies.[1] Concern about this interference in the immune response to SARS-CoV-2 might have led physicians to reconsider the treatment strategy for less effective drugs, which is also problematic.[2]

Multiple Sclerosis (MS) is currently the most studied immune-mediated neurological entity concerning SARS-CoV-2 infection, with several national cross-sectional studies published until now.[3–5] Overall, MS patients present a similar incidence, risk factors, and outcome profile compared to the general population.[6] Concerns about immunotherapies have been reviewed by several groups[1,7–9], considering the pathophysiological mechanism underlying the viral infection and the limited clinical evidence. The majority of the therapeutic alternatives used in MS appear to be safe[8,10], with some of which even having a potential protective effect, namely interferon (IFN).[7,11] Anti-CD20 (rituximab or ocrelizumab), however, were related to more severe forms of COVID-19 in some studies[3,5,7,8].

There is a lack of consistent data concerning other neuroimmunological disorders such as chronic inflammatory polyneuropathies or myasthenia gravis (MG), despite sharing common features and treatment approaches.[12]

This study aims at characterizing SARS-CoV-2 infection in patients followed in the neuroimmunology outpatient clinic of a tertiary centre from the north of Portugal.

2. Methods

This is a retrospective study on a cohort of neuroimmunological patients, conducted at Centro Hospitalar Universitário do Porto (CHUPorto) in Porto, during the observational period of 20 months (March 2020 to November 2021).

2.1 Study Population

All patients followed in our neuroimmunology outpatient clinic were asked at their routine appointment (at least every 6 months) if they had been tested positive for SARS-CoV-2 since their last visit. All patients with a confirmed SARS-CoV-2 infection were invited to participate after informed and written consent.

A positive reverse transcriptase-polymerase chain reaction (PCR) on nasal and/or pharyngeal swab was considered a confirmed infection. This was further verified in the national electronic database before enrolment. Included patients were then interviewed by phone.

2.2 Sample characterization

Data was retrospectively collected from the electronic clinical charts and completed with the information given by the patient in the telephonic interview. The day of symptoms appearance was considered as the baseline.

We collected demographic data, including sex, age, body mass index (BMI), smoking and drinking habits, and other comorbidities. Comorbidities were categorized as follows: pulmonary disease, cardiovascular disease, arterial hypertension, diabetes mellitus, chronic liver disease, chronic renal disease, HIV, depression, other autoimmune diseases, and overweight (defined as a body mass index > 25 kg/m2). COVID-19 data included disease-associated signs and symptoms, hospitalization, pneumonia and respective severity (according to radiological examinations and ventilation support), therapies directed at COVID-19 (e.g., dexamethasone, remdesivir, and antibiotics), intensive care unit (ICU) admission, and recovery or death. COVID-19 severity was classified according to a Portuguese national guideline (norma 004/2020): (1) mild disease, if the patient had mild symptoms without pneumonia or hypoxemia; (2) moderate disease, if the patient had pneumonia without oxygen desaturation (≥90%) or hemodynamic instability; (3) severe disease if they presented oxygen desaturation (<90%), respiratory frequency >30 cycles per minute, respiratory difficulty or signs of hemodynamic instability; (4) critical disease if they presented acute respiratory distress syndrome with septic shock.

Neurological disease-specific data was collected. For MS, this included disease onset date, course[13] (relapsing-remitting MS [RRMS] or progressive MS [PMS], which

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included primary progressive MS [PPMS] or secondary progressive MS [SPMS]), Expanded Disability Status Scale (EDSS), DMT at the date of COVID-19 symptoms started, and the date of last treatment dose. For MG, we included the disease type and immunosuppressive therapy at the date COVID-19 symptoms started, and date of last treatment dose. We proceed accordingly for the other disorders, using the appropriate classification based on current guidelines.[14–18].

Patients were classified as having received or not a cycle of methylprednisolone at least three months before the COVID-19 infection. Regarding DMT, we defined two groups: immunomodulators (IFN-beta and GA) and immunosuppressors, which included the other treatment regimens. Patients on oral prednisolone in a dose >10 mg/day were also considered on immunosuppressors.[19] Lymphopenia was defined as an absolute lymphocyte count (cell/m3) <1000.

Clinical evaluation from the visit immediately after the infection was compared with the most recent assessment before the first positive SARS-CoV-2 test. Outcome at the moment of analysis (recovered, worsened, or death) was collected.

2.3 Statistical Analysis

For cohort description, qualitative variables were presented using the absolute and relative frequencies, while for the quantitative variables, the mean and standard deviation, or median and interquartile range (p25 − p75) (IQR), was calculated according to the normality of the distribution.

For comparing quantitative variables between groups based on disease severity, we used the Student's t-test or the Mann-Whitney U-test, according to the variable presenting a normal distribution or not, respectively. A $\chi 2$ test was used for qualitative variables, with post hoc Bonferroni analysis of adjusted standardized residuals when appropriate. Willcox test was used to compare the median Karnofsky score before and after the infection and the EDSS in the subgroup analysis of MS patients.

Statistical analysis was conducted using IBM Statistical Package for the Social Sciences (SPSS; version 27, Armonk, NY, USA).

A p value < 0.05 was considered significant.

2.4 Ethical Considerations

This project was approved by CHUPorto ethics committee. Patient informed and written consent were obtained.

3. Results

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The cohort comprised 1795 patients followed at the neuroimmunology outpatient clinic, of whom 91 had confirmed SARS-CoV-2 infection (5.1 %).

Sixty-two patients (68.1%) were female, with a mean age of 48.9±16.7 years. The median disease duration was 11.0 (IQR 6.0-19.0) years. Table 1 shows the sample characterization. A body mass index (BMI) > 25kg/m^2 defined overweight and was the most common comorbidity (mean BMI of 25.7 (9.0) kg/m^2), present in 38.5%, followed by arterial hypertension in 24.2% and depression in 19.8%. Fourteen patients (15.4%) had other autoimmune disorders, most of which comprised autoimmune thyroiditis (8 cases).

Sixty-one patients (67.0%) had MS, of which 50 had RRMS (54.9%) and 11 PMS (12.1%); twelve patients (13.2%) had MG. Six patients (6.6%) were followed for autoimmune encephalitis and 6 (6.6%) for chronic inflammatory demyelinating polyneuropathy (CIDP). Six patients (6.6%) were classified as having other diseases, which included one case of each of the following: neuromyelitis optica spectrum disorder (NMOSD), neurosarcoidosis, Tolosa-Hunt syndrome, neuro-lupus, central nervous system vasculitis, and an unclassified inflammatory disease of the central nervous system.

Concerning therapy, 76 (83.5%) of patients were under DMT, of which 77.6% were on immunosuppressants. As shown in table 1, anti-CD20 monoclonal antibodies (rituximab or ocrelizumab) (13.2%) and prednisolone (12.1%) were the most common DMT used. The laboratory values from at least one year before SARS-CoV-2 infection were available in the clinical records of 60 patients (65.9%), of which 21 (23.1%) had lymphopenia. Six of these patients were taking sphingosine 1-phosphate inhibitors.

Thirteen patients (14.3%) were asymptomatic and tested in the community setting for screening purposes. The most common symptoms were fatigue (60.4%), anosmia (51.6%), ageusia (50.5%), cough (49.5%) and 42.9% had fever. Most patients had mild disease (84.6%), with 4 cases (4.4%) of moderate disease, 3 cases (3.3%) of severe disease and 7 cases (7.7%) of critical disease being reported. Seven patients received remdesivir (7.7%) and 10 prednisolone (11.0%) as treatment for the acute infection. Clinical recovery was the most common outcome, with a total of 85 (93.4) patients considered recovered or recovering after a mean follow-up of 7.5±2.7 months after the infection. In total, 13 patients were hospitalized (14.3%), and 4 deaths occurred because of COVID-19 infection (3.7%). The use of immunosuppressants (n=8) was not associated with hospitalization (p=0.764), neither the use of anti-CD20 (n=2) (p=0.679).

Three hospitalized patients had received a cycle of methylprednisolone in the previous three months (p=0.058). The patients that died had the following characteristics: 1) A 45-year-old female with RRMS taking rituximab (*off-label*); 2) An 82-year-old female with unclassified inflammatory disease of the CNS on methylprednisolone cycles, the last less than three months before the infection; 3) A 78-year-old male with anti-NMDAR encephalitis on cyclophosphamide and methylprednisolone cycles, the last less than three months before the infection; 4) An 88-year-old female with LOMG taking prednisolone 2.5 mg/day.

Regarding vaccination, 90.1% of our sample was immunized in November 2021. Fifteen cases (16.5%) occurred after receiving the complete vaccination scheme during this period, all of which corresponding to mild COVID-19.

The mean Karnofsky score before the infection was 80.0 (IQR 70.0-100.0), which was significantly higher than the score after the infection (p=0.004). A subanalysis of the MS patients showed that the mean EDSS value before and after the infection (both 2.0, IQR 0.0-8.0) was not significantly different (p=0.593).

We then compared groups based on disease severity (mild to moderate *versus* severe to critical) (Table 2). Patients with severe to critical disease (n=10, 11.0%) had a mean age of 69.4±21.0 years which was significantly older than patients with mild to moderate disease, 46.5±14.4 years (p<0.01).

Alcohol consumption, smoking, the presence of one or more comorbidities (including overweight), or preceding lymphopenia did not differ significantly between groups. The neuroimmune disorders were significantly different between groups (p<0.01). A post hoc Bonferroni analysis of adjusted standardized residuals showed that MG was associated with more severe disease (p=0.02). EMRR was significantly more represented in the mild to moderate COVID-19 group (p=0.002). Other conditions' distributions did not differ significantly. One patient with neurosarcoidosis and another with unclassified inflammatory disease of the central nervous system developed critical disease.

Regarding treatment, 67 (73.6%) patients in the mild to moderate disease group and 9 (9.9%) in the severe to critical were on DMT, specifically, immunosuppressants in 53 (58.2%) and 6 (6.6%), respectively, which was not significantly different. This included 4 patients on prednisolone in a dose greater than 10 mg/day. Ten patients (11.0%) in the first group and 2 patients (2.2%) in the second were on anti-CD20, which was also not significantly different. Receiving methylprednisolone in the 3 months before tended to

associate with a worse outcome, with 2 patients submitted to this treatment belonging to the more severe COVID-19 group (p=0.17).

4. Discussion

Our study included 91 patients with confirmed SARS-CoV-2 infection during the observational period that extended 20 months after the first reported case of COVID-19 in Portugal (March 2020). Most of the reported cases date to the last trimester of 2020, consistent with the second wave of COVID-19 in Portugal as in other European countries.[20] In the last year, several publications have appeared reporting outcomes and risk factors associated with COVID-19 infection in patients with MS, with few studies in populations of patients with others immune-mediated neurological disorders.[21,22] Despite the particularities of each disease, some neuroimmunological diseases share similarities in terms of clinical-demographic characteristics and treatments used (like: corticosteroids and immunosuppression therapy).To our knowledge, this is the first study to include patients with various neuroimmunological disorders treated in a tertiary referral centre.

Similar to other studies in the general population[23] and in MS cohorts[24], older age was a factor related to disease severity in our cohort. We found no association between individual comorbidities or number of comorbidities and outcome, despite what was shown by previous studies with more representative samples.[3,25] In the Turkish MS cohort, the presence of comorbidities was also not related to increased severity.[26] Overall, we believe that these results may be explained by the reduced prevalence of comorbidities in our cohort. Only one patient had cardiovascular disease, which was reported previously as the comorbidity with the most significant correlation with severity (OR 5.72 (2.39-13.66)).[25] Moreover, our population had a mean BMI of 25.7 (9.0) kg/m^2, which is lower than previously reported, probably also accounting for the difference between studies.[3] Furthermore, we used a cut-off ≥ 25 kg/m^2 to define weight-excess, which differs from other studies that used the cut-off of obesity (30 kg/m^2).[3]

In the group of MS patients (50 patients, 67.0%), the RRMS was significantly more present in the mild to moderate COVID-19 group (p=0.001), even if no association was found between disease course (RRMS vs PMS) and COVID-19 severity or outcome, as previously suggested.[5,24]. MG was the second most common condition, present in 12.2%, and it was associated with more severe infection (p=0.002). A tendency towards more severe infection has also been reported in a Brazilian cohort.[21] The putative

association of MG and worse COVID-19 could be explained by the possibility of greater respiratory fatigue in these patients or even by a recently suggested cholinergic disfunction associated with COVID-19.[27] In fact, one of the four casualties was on a late-onset MG patient. Nevertheless, none of our patients developed myasthenic crisis secondary to the infection, contrasting with a reported occurrence of as high as 40%.[28] More studies with larger samples are needed to better address this issue.

In this cohort, thirteen patients (14.3%) were hospitalized, 4 (4.4%) in intensive care units, with 4 reported deaths during this period (4.4%). Among the patients that have died, only one was an MS case, which prevents us from comparing with the reported death rate in literature. This value was still similar to that obtained by Louapre C. *et al*. (3.5%).[25]

National data from the same period indicate that 431700 COVID-19 cases occurred in the northern region of Portugal, with 5645 confirmed deaths translating in 1.3% mortality rate, which is lower compared to our cohort.[29] This finding is consistent with some studies that have found higher mortality in patients with neurological diseases with COVID-19, namely patients with MS and MG, than in the general population with COVID-19[28,30], but there are studies that have not found this association[31,32] Using the Portuguese national guideline, 11% of patients were classified as having severe or critical disease, similar to some MS cohorts.[33] However, other studies report values of 21.0[25] and 23.7%[24], which may reflect sample size differences and the criteria used to define severe/critical COVID-19.

The level of independence in daily activities measured by the Karnofsky performance status, was affected by the infection. Despite this scale not being adapted to neurological conditions[34], we opted to use it given the diagnostic variability of our sample. On the other hand, the EDSS was not significantly impacted, which may reflect relatively low baseline EDSS scores (2.0) in a majority of RRMS patients.

We found no association between DMT and COVID-19 severity, despite most of our cohort being on immunosuppressive treatment at the time of the infection, as were 6 of the 9 patients with severe to critical COVID-19. Other small MS cohorts from New York[24], Turkey[26], and Egipt[33] have also found no association between DMT and disease course. Current knowledge on the mechanisms of DMT and SARS-CoV-2 pathophysiology support these findings.[8] The most common DMT in our sample were DMF and first-line injectables (11.0%), which have been associated with no risk of higher risk of severe COVID-19.[5,8] Our cohort included patients with other conditions

besides MS, for which other immunosuppressive drugs are used, such as mycophenolate, methotrexate, azathioprine, cyclophosphamide, and prednisone. These agents have been previously implicated as associated with severity.[35]

Contrasting with our findings, other studies with larger samples show conflicting results.[36] In Covisep[25], the authors found that immunosuppressive DMTs were associated with a 4.2-times higher risk of severe COVID-19 than INF-beta or GA, in a sample of 347 patients. Likewise, in the Italian MuSC-19[5] national registry of 844 (suspected or confirmed) cases, anti-CD20 were associated with 2.6 times greater risk of severe disease when compared to DMF, adjusted to other variables. The CoviMS[3] of North America (1626 patients with suspected or confirmed infection) found that the risk of hospitalization was increased with ocrelizumab and rituximab, by 1.6 and 4.6 times, respectively. More recently, Simpson-Yap and colleagues[36] aggregated data from 28 countries resulting in 657(28.1%) suspected and 1,683(61.9%) confirmed COVID-19 cases – 49.6% of the sample belonged to the previously referred CoviMS registry[3]. In this study, and compared to DMF, anti-CD20 were associated with increased hospitalization and intensive care admission, adjusting for age, disease course and EDSS. Rituximab specifically was also associated with artificial ventilation (aOR=6.15, 95%CI=3.09-12.27). The authors found that this was not a function of more regular hospital attendance since natalizumab was not associated with these adverse outcomes. The mortality rate in this study (4.4%) was similar to our cohort but different from that obtained in Musc-19[5], where older patients (≥70 years) were more represented (17.7% of the cohort).

Our study has several limitations that must be accounted for. First, this is a single-center cohort with limited sample size, preventing further comparisons. Particularly, only ten patients (11.0%) developed severe or critical COVID-19, representing a heterogeneous group of entities (1 with MS, 4 with MG, and 5 with other neuroimmunological diseases) treated with different classes of immunosuppressants. The small sample size prevented us from pursuing multivariate analysis and might explain the difference between ours and other small cohorts and the larger registries in terms of correlation between DMT and outcome. Second, this was a retrospective study, and many of the patients diagnosed with mild COVID-19 had no recent laboratory analysis from which we could appreciate lymphopenia. Third, the use of the Karnofsky performance status is not adapted to neurological disorders. However, this is one of the most commonly used scales to assess patients' quality of life and has been used in studies with patients with

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CNS or PNS disorders.[37,38] The need for a uniform, simple and well-known method for analyzing patient functionality was the main reason for choosing this scale. Fourth, it It would be interesting to include MRI for MS patients to detect imagological evidence of disease activity after the infection. We decided not to include this data since most patients had neither follow-up MRI or the last MRI was done more than one year before SARS-CoV-2 infection. Finally, patients without PCR proven SARS-CoV-2 infection were not included in the analysis, which could have led to under-reporting of non-hospitalised patients that where not tested due to limited access to testing kits in the initial stages of the pandemic.

5. Conclusion

We found that older age and MG were associated with COVID-19 severity in this Portuguese single-centre cohort of neuroimmunological disorders. We found no association between a specific DMT, including anti-CD20, and outcome. This may be related to the small number and clinical heterogeneity of the more severe COVID-19 cases preventing further comparisons.

Overall, 93.4% of the population had a favourable outcome, achieving recovery after the infection. However, the mortality rate was greater than that for the general population from the same region, replicating previous studies.

Recognizing the risk factors for severe COVID-19 in patients with neuroimmunological disorders could help to improve treatment decision making and appropriate monitoring strategies. More studies are needed to specifically address the impact of immunosuppressants on COVID-19 severity and the effects of the SARS-CoV-2 infection in the long term in this subset of patients.

CRediT author statement

João Moura and **Henrique Nascimento** performed Investigation, Data Curation, Formal analysis, and Writing - Original Draft

Inês Ferreira, Raquel Samões, Catarina Teixeira, Dina Lopes, Daniela Boleixa, Ana Paula Sousa, Ernestina Santos performed Investigation, Resources and Writing - Review & Editing

Ana Martins Silva performed Conceptualization and Writing - Review & Editing

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Table 1 – Characterization of the patients with neuroimmunological disorders infected with SARS-CoV-2.

Characteristics		N
Age, mean (SD)		48.9 (16.7)
Female, n (%)		62 (68.1)
Education (years), mean (SD)		11.6 (4.8)
Smoking, n (%)		
	Current	13 (14.3)
	Previous	11 (12.1)
Alcohol, n (%)		
	Ocasional	28 (39.8)
	Regular	5 (5.5)
Disease duration (years), median (IQR)		13.1 (6.0-19.0)
Diagnosis		
Multiple Sclerosis, n (%)		61 (67.0)
	RRMS	50 (54.9)
	PMS	11 (12.1)
Myasthenia Gravis, n (%)		12 (13.2)
	EOMG	5 (5.5)
	LOMG	2 (2.2)
	Thymoma associated	2 (2.2)
	AntiMusk	2 (2.2)
	Seronegative	1 (1.1)
CIDP, n (%)		6 (6.6)
	DADS	2 (2.2)
	MMN	3 (3.3)
	MADSAM	1 (1.1)
Autoimmune encephalitis, n (%)		6 (6.6)
	NMDAr	1 (1.1)
	GAD-65	2 (2.2)
	Seronegative	3 (3.3)
NMOSD, n (%)		1 (1.1)
Systemic diseases with CNS involvement		2 (2.2)
	Neurolupus	1 (1.2)
	Neurosarcoidosis	1 (1.2)
Others*, n (%)		3 (3.3)
Karnofsky score		
Previous, median (IQR)		80.0 (70.0-100.0)
Current, median (IQR)		80.0 (70.0-100.0)
Treatment, n (%)		
	Anti-CD20	12 (13.2)
	Prednisolone	11 (12.1)
	First line injectables	10 (11.0)
	DMF	10 (11.0)
	AZA	9 (9.9)
	S1PM$^{\#}$	8 (8.8)
	MTP < 3 months	7 (7.7)
	Teriflunomide	6 (6.6)
	IgEV	5 (5.5)
	Natalizumab	4 (4.4)
	Cladibrine	2 (2.2)
	MTX	3 (3.3)
	Alemtuzumab	1 (1.1)
	MMF	1 (1.1)
	CYC	1 (1.1)
Comorbidities, n (%)		total

	Overweight	35 (38.5)
	Arterial hypertension	22 (24.2)
	Depression	18 (19.8)
	Autoimmune diseases	14 (15.4)
	Diabetes mellitus	4 (4.4)
	Chronic renal disease	4 (4.4)
	Chronic liver disease	2 (2.2)
	Cardiovascular	2 (2.2)
	HIV	1 (1.1)
Available laboratory values before COVID-19, n (%)		60 (65.9)
	Lymphopenia	21 (23.1)
Symptoms COVID-19, n (%)		
	Fatigue	55 (60.4)
	Anosmia	47 (51.6)
	Ageusia	46 (50.5)
	Cought	45 (49.5)
	Fever	39 (42.9)
	Headache	37 (40.7)
	Arthralgias	34 (37.4)
	Nasal congestion	25 (27.5)
	Dyspnoea	19 (20.9)
	Odynophagia	18 (19.8)
	Assymptomatic	13 (14.3)
Disease severity, n (%)		
	Mild	77 (84.6)
	Moderate	4 (4.4)
	Severe	3 (3.3)
	Critical	7 (7.7)
COVID-19 directed treatment, n (%)		11 (12.1)
	Remdesivir	7 (7.7)
	Corticotherapy	10 (11.0)
Outcome, n (%)		
	Recovered/recovering	85 (93.4)
	Worsened	2 (2.2)
	Dead	4 (4.4)

AZA – azatioprine; CIDP – chronic inflammatory demyelinating neuropathy; CYC – cyclophosphamide; DADS - distal acquired demyelinating symmetric neuropathy; ; DMF – dimethyl fumarate; EOMG – Early Onset Myastenia Gravis; IQR – interquartile range; IvIgEV – intravenous immunoglobulin; LOMG – Late Onset Myastenia Gravis; MADSAM - multifocal acquired demyelinating sensory and motor neuropathy; MMF – mycophenolate mofetil; MMN – multifocal motor neuropathy; MS - multiple sclerosis;; MTP – methylprednisolone; MTX – metotrexate; NMOSD – neuromyelitis optica spectrum disorders; RRMS – relapsing remitting MS; PMS – progressive MS SD - standard deviation; S1PM - Sphingosine 1-phosphate receptor modulators
* - Others include: 1 CNS vasculitis, 1 unspecified CNS inflammatory disease, 1 Tolosa-Hunt sydrome.
[#] - Includes 7 patients on fingolimod and 1 patient on posenimod

Table 2 – Comparison of patients with neuroimmunological disorders divided according to COVID-19 severity.

Characteristics		Disease severity		
		Mild-moderate 81 (89.0%)	Severe-critical 10 (11.0%)	P
Age, mean (SD)		46.5 (14.4)	69.4 (21.0)	**<0.01**
Smoking, n (%)		23 (25.3)	1 (1.2)	0.25
Regular alcohol, n (%)		5 (5.5)	0	0.12
Disease duration in years, median (IQR)		11.5 (6.0-20.5)	7.5 (7.0-11.0)	0.16
Diagnosis, n (%)				
	MS	60 (65.9)	1 (1.2)	**<0.01**
	MG	8 (8.8)	4 (4.4)	

	CIDP	5 (5.5)	1 (1.2)	
	AE	4 (5.5)	2 (2.2)	
Treatment				
	DMT	67 (73.6)	9 (9.9)	1.00
	Immunosuppressants	53 (58.2)	6 (6.6)	0.73
	Immunomodulators	11 (12.1)	0	0.60
	Anti-CD20	10 (11.0)	2 (2.2)	0.62
	MTP < 3 months	5 (5.5)	2 (2.2)	0.17
Comorbidities, n (%)				
	≥ 1	35 (38.5)	8 (8.8)	0.06
Lymphopenia before infection, n (%)		20 (22.0)	1 (1.2)	0.26
Outcome, n (%)				
	Worsened	0	2 (2.2)	**0.03**
	Dead	0	4 (4.4)	

AE - autoimmune encephalitis; CIDP – chronic inflammatory demyelinating neuropathy; DMT – disease modifying treatments; IQR – interquartile range; MG - Myasthenia Gravis; MS - multiple sclerosis; MTP – methylprednisolone; NMOSD – neuromyelitis optica spectrum disorders; PPMS – primary progressive MS; RRMS – relapsing remitting MS; SD - standard deviation; SPMS – secondary progressive MS.

* - Others include: 1 neuromyelitis optica spectrum disorder, 1 CNS vasculitis, 1 neurosarcoidosis, 1 neurolupus, 1 Tolosa-Hunt Syndrome, 1 unspecified CNS inflammatory disease (the latter with COVID-19 critical illness).

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